Scientific Abstract

"Restenosis" is the term which has been used to denote *recurrent* narrowing of a blood vessel after an initially successful revascularization procedure, such as percutaneous transluminal angioplasty (PTA). Despite the fact that PTA has now been used widely to treat atherosclerotic obstructions in the coronary and peripheral arterial circulations for nearly three decades, restenosis continues to be a vexing, and consequently expensive, complication of this otherwise efficacious intervention.

In certain regions of the circulatory system, the incidence of restenosis has been so high that it has seriously limited enthusiasm for the application of PTA. The superficial femoral artery (SFA)/popliteal artery of the leg constitutes one such site. While the acute procedural success for percutaneous revascularization of lesions in the SFA using conventional guidewires and standard PTA is well in excess of 90%, published reports have established that restenosis may complicate the clinical course of as many as 60% of patients undergoing PTA for obstruction of the SFA.

Given that disease of the SFA represents one of the most frequent sites of peripheral vascular obstruction, the disappointing durability of PTA for SFA lesions has serious implications. While bypass surgery may be often used to successfully treat these patients, such surgery is not risk-free, particularly in a population of patients with a high frequency of co-morbid diseases, including coronary and carotid disease. The cost, recuperation time, and frequent requirement for a patient's native veins (the supply of which is fixed and the need for which may extend to coronary bypass or repeat lower extremity bypass surgery) as conduits constitute additional liabilities of SFA bypass surgery.

Previous strategies to limit the development of restenosis by non-mechanical means have employed anti-proliferative, anti-platelet, anti-coagulant, anti-inflammatory, spasmolytic, and lipid-lowering therapies; none have proved to be effective. Curiously, despite: a) the fact that PTA routinely produces extensive endothelial denudation, and b) the accepted roles of the endothelium in providing barrier function, reducing thrombogenicity, and inhibiting restenosis, treatment strategies designed specifically to restore endothelial integrity have not been previously explored for restenosis prevention.

In an attempt to improve upon the results of SFA/popliteal PTA, we have therefore considered that acceleration of re-endothelialization may be achieved following administration of mitogens which promote endothelial cell migration and/or proliferation. These include vascular endothelial growth factor (VEGF). The rationale and experimental findings for administration of recombinant protein and/or the gene encoding VEGF in 2 different animal models are outlined in the accompanying manuscripts attached to this proposal. Briefly, these studies demonstrate that VEGF accelerates re-endothelialization and thereby reduces intimal thickening.

Accordingly, **the purpose of this clinical protocol is to document the safety of interventional re-endothelialization achieved in this case by percutaneous catheter-based delivery of the gene encoding vascular endothelial growth factor (VEGF) in patients with claudication due to SFA obstruction. A secondary objective is to investigate the bioactivity of this strategy for inhibiting restenosis.**

Plasmid DNA encoding for the 165-amino acid isoform of VEGF will be delivered post-PTA using a hydrogel-polymer coated balloon angioplasty catheter, in the absence of associated viral or other vectors. Patients will be studied pre- and post-PTA by a variety of non-invasive and invasive tests for evidence of safety as well as bioactivity. This preliminary study may yield evidence that gene therapy designed to accelerate re-endothelialization at the site of PTA-induced endothelial disruption may represent a novel strategy for inhibition of restenosis in peripheral as well as coronary artery disease.